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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BANNER & WITCOFF, LTD.
TEN SOUTH WACKER DRIVE
SUITE 3000
CHICAGO, IL 60606

EXAMINER	
POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,909	BRON, DENIS	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,9-11,13-15,17-19,21-25 and 27-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-11,13-15,17-19,21-25 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/11/2009; 04/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/28/2009 has been entered.

Claims 4, 7, 8, 12, 16, 20, and 26 have been cancelled. Claims 21, 22, 24, and 28 have been amended to remove dependency from the cancelled claims.

Applicant submits that he cancelled claims 9, 10, 13, 14, and 18 in the reply filed on 04/28/2009. However, the claim listing identifies claims 9, 10, 13, 14, and 18 as "previously presented".

Claims 1-3, 5, 6, 9-11, 13-15, 17-19, 21-25, and 27-29 are pending and under examination.

2. The objection to claims 22-25 and 28 is withdrawn in response to Applicant's amendments to the claims filed on 04/28/2009.

Priority

3. Applicant argues that the foreign priority document EPO 0201499.0 provides support for the use of the NCAM Ig loop domains I, II, and III and the use of an

integrase (p. 2, line 5 through p. 4, line 13). This argument is not found persuasive because the indicated passage only recites a transposase (such as Sleeping Beauty) and not an integrase; while the use of a transposase could result in integration into the genome, a transposase is not the same with an integrase. Furthermore, the indicated passage does not mention the integrase from the phiC31 bacteriophage or the NCAM Ig loop domains I, II, and III. Even the instant specification makes the distinction between transposases and integrases (see p. 3, line 23 through p. 4, line 6).

Regardless, it is noted that the arguments are moot, because no intervening art was used to reject the instant claims.

Information Disclosure Statement

4. Applicant argues that an English translation of the DE 100 56 136 can be found at PGPUB 2004/0191303. In response to this argument, it is noted that PGPUB 2004/0191303 is not related to the instant application. If Applicant wishes the DE 100 56 136 document be considered, Applicant must submit an English translation in the present application.

Claim Rejections - 35 USC § 112, new matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". Specifically, the amendment to the claim to include the term “a DNA integrase activity” is considered new matter.

As amended claim 1 recites the use of "a DNA integrase activity or a molecule encoding such a DNA integrase activity”. It is clear from the claim language that the "DNA integrase activity" is the protein. It is noted that the specification only provides support for the use of a nucleic acid encoding an integrase; there is no support for the use of the protein (see p. 4, lines 1-13). A search of the remaining portions of the specification failed to provide literal support for the use of integrase protein.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition

to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

Applicant argues that the DNA integrase activity disclosed in the application is a DNA encoding the integrase and not necessarily being the integrase protein (see EPO 02014991.0, p. 3, lines 6-15, p. 4, lines 17-18, p. 5, lines 30-33). Therefore, Applicant argues, the rejection should be withdrawn.

Applicant's argument has been considered, however, the rejection is maintained for the following reasons:

Claim 1 recites in alternative "a DNA integrase activity or a molecule encoding such a DNA integrase activity". It is clear from the claim language that the "DNA integrase activity" is the protein and that the "molecule encoding the DNA integrase activity" is the nucleic acid. Therefore, the claim clearly encompasses a delivery system comprising either the integrase as a protein or a nucleic acid encoding the integrase. The embodiment of a delivery system comprising the integrase as a protein is not supported by the instant specification or by the priority document EPO 02014991.0. Applicant points to the priority document EPO 02014991.0 as providing support. As

noted above, the priority document does not provide support for the use of an integrase either as a protein or as a nucleic acid.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3, 5, 6, 22, 23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. (PGPUB 2005/0037445, of record), in view of each Maurer et al. (Expert Opin Biol Ther, 2001, 1: 923-947, of record), Groth et al. (Proc. Natl. Acad. Sci. USA, 2000, 97: 5995-6000, of record), Schreier et al. (J Biol Chem, 1994, 269: 9090-9098, of record), and Ranheim et al. (Proc Natl Acad Sci USA, 1996, 93: 4071-4075, of record).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface; the system could further comprise a peptide providing nuclear localization

signal coupled to the cDNA (claims 1, 5, 6, 22, and 23) (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 37, paragraphs 0463 and 0464, p. 39, paragraphs 0563-0565, 0570, 0571, and 0577, p. 54, paragraph 0824). Poulsen et al. teach that the cDNA could be a PNA, i.e., they teach PNA-linked peptide (claim 23) (p. 6, paragraph 0099). Poulsen et al. also teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (claim 1) (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach targeting liposomes by using an NCAM fragment comprising the IgI and IgII domains or an NCAM fragment comprising IgIII domain as targeting ligands, they do not teach using a fragment comprising all IgI, IgII, and IgIII domains of NCAM (claim 2). However, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by combining their IgI, IgII, and IgIII domains into one fragment for increased binding to NCAM on the target cell surface, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the art teaches that, beside the IgI and IgII domains, the IgIII domain also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Poulsen et al., Maurer et al., and Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claims 1 and 27). However the prior art teaches site-specific integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific

integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Poulsen et al., Maurer et al., Ranheim et al., and Groth et al. do not teach linking the NCAM via a hydrophobic anchor molecule (claim 3). However, such is suggested by the prior art. For example, Schreier et al. teach targeting liposomes to specific cells by inserting ligands into liposomes via a glycosylphoshaphatidylinositol (GPI) anchor (i.e., a hydrophobic anchor molecule) (Abstract, p. 9092, columns 1 and 2, p. 9093, columns 1 and 2, p. 9097, column 1, paragraph bridging column 2, 9098, column 1, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by inserting the NCAM ligand via a GPI anchor, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schreier et al. teach their method as simple and convenient (p. 9090, column 2, first full paragraph). One of skill in the art would have been expected to have a reasonable expectation of success

because the art teaches the successful use of GPI anchors to incorporate proteins into liposomes.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Poulsen discloses targeting complexes that are capable of being internalized into cells. The targeting complexes include at least one binding partner to associate with a cell surface molecule, and a bioreactive species. (paragraphs [0079] and [0087]). As recognized by the Examiner, Poulsen does not specifically teach liposomes comprising DNA as a bridge between a nucleic acid and a targeting moiety. In other words, Poulsen does not teach liposomes comprising DNA in their internal compartment and having the cell adhesion molecule NCAM or a fragment thereof. Further, Poulsen is silent regarding targeting complexes that comprise "a DNA integrase activity or a molecule encoding such a DNA integrase activity" as claimed in claim 1. Applicant argues that none of Maurer, Groth, Schreier or Ranheim remedy the deficiencies of Poulsen with respect to liposomes comprising DNA integrase activity.

Maurer is directed to a review of liposomes for drug delivery and discusses only conventional drugs, DNA and pDNA (Abstract and page 936, column 1 through page 941, column 1). Maurer is thus completely silent regarding DNA integrase activity. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM. Ranheim is directed to the interaction of neural cell adhesion molecules (NCAM) on two different cells and is totally unrelated to DNA integrase activity (Abstract). Schreier is directed to glycosylphosphatidylinositol-

anchored proteins for use as targeting molecules for liposomes, and is entirely silent regarding DNA integrase activity (Abstract). Consequently, it would not have been obvious for one of skill in the art to develop the invention of claim 1merely from the disclosures of Poulsen, Maurer, Groth, Schreier and Ranheim. Claim 1 is therefore patentable over Poulsen in view of Maurer, Groth, Schreier and Ranheim. Applicant submits that the Office Action is silent regarding how the application of the Graham factors would demonstrate the obviousness of claim 1. One of skill in the art would not have been motivated to make the proposed modifications of Poulsen because it was only in the Applicant's disclosure that it was recognized that liposomes comprising a pharmaceutical agent (such as a DNA encoding human dystrophin) in their internal compartment, NCAM linked to their external surface, and a DNA integrase activity or a molecule encoding such a DNA integrase activity could be useful.

The present case is similar to Sanofi-Synthelabo v. Apotex Inc., 550 F3d 1075 (Fed. Cir. Dec. 12, 2008). In Sanofi, the Federal Circuit affirmed a lower court holding of nonobviousness. In doing so, the Federal Circuit stated that "[t]he determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim," citing KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007). The Federal Circuit further held that "[f]or chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. See In re Sullivan, 498 F.3d 1345, 1353 (Fed. Cir. 2007); In re Papesch., 315 F.2d 381, 391 (CCPA 1963)." In Sanofi, while it was known that different enantiomers of a compound "can exhibit different biological activities," it was also clear

from the record that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested." The record demonstrated that there was no known scientific principle that allowed prediction of the degree to which stereoisomers would exhibit different levels of therapeutic activity and toxicity. The record also demonstrated that two properties (i.e., activity and toxicity) were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity. Witnesses also explained that it was known that for compounds whose biological activity is delivered through metabolism within the body, the acid environment in the stomach or other metabolic processes often restores the racemic state, thereby removing any potential benefit of a separated enantiomer. On the basis of the trial evidence, the district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the anti-platelet activity and none of the adverse neurotoxicity. The Federal Circuit held that clear error had not been shown in this finding, and in the conclusion of nonobviousness based thereon, again citing Papesch, 315 F.2d at 391 (a chemical compound and its properties are inseparable). In the present case, it is clear from the record that it was not predictable whether modifications of Poulsen as proposed in the Office Action would exhibit different biological activities, and it was also not predictable whether any differences, if any, would be weak, moderate, or strong, or how they would be manifested. The record demonstrates that there was no known scientific principle that allowed prediction of the degree to which different forms of liposomes would exhibit different levels of therapeutic activity. On the basis of this

evidence, a person of ordinary skill in this field would not reasonably have predicted that the claimed invention would provide the results of the present invention. The results of the present invention are shown in the accompanying Scientific Report, entitled "Development of Novel Non-Viral Vectors for Gene Therapy of Muscular Diseases," of which the Applicant is an author. The accompanying Scientific Report shows that the use of NACM efficiently enhances the uptake of a plasmid into muscle cells. In this specific experiment, the P2 peptide, being derived from the second Ig domain of NCAM, was coupled to biotin. Furthermore, biotin was also linked to the outer surface of the liposome. By using streptavidin, which binds to biotin, P2 was linked to the liposome. When exposed to the cell line (C2C12, ATCC Number CRL-1772), the P2 peptide was able to mediate the uptake of plasmid DNA, coding for Renilla Luciferase, from liposomes. As a result, the transformed cells expressed Renilla Luciferase and gave a positive signal in a subsequent luciferase assay. However, a liposome without a targeting molecule was not able to efficiently transform the cell line; nor did the sample where the P2:Streptavidin ratio reached 2.5:1. In the latter case, P2 saturates the binding sites of streptavidin, hence the coupling of P2 to the liposome via streptavidin-biotin-interaction is not possible or occurs only in an ineffective manner.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to this argument, it is noted that the instant rejection is an obviousness-type rejection which is based on a combination of references; it is the combination of reference which teaches the claimed delivery system. Because the instant rejection is an obviousness-type rejection, none of the cited references has to teach each and every claim limitation; if they did, the rejection would have been anticipation and not an obviousness-type rejection. It is noted that, apart from asserting that one of skill in the art would not have been motivated to combine the cited art, Applicant did not provide any argument or evidence demonstrating such. For these reasons, Applicant's arguments directed to the references individually are not found persuasive.

Applicant argues that the Examiner did not indicate how the application of the Graham factors would demonstrate obviousness. This is incorrect. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Determining the scope and the content of the prior art entails understanding the invention, what to search, and where to search; Applicant does not argue that the

Examiner did not understand the rejection or did not know what or where to search. Ascertaining the differences between the claimed invention and the prior art entails interpreting the claim language and considering both the invention and the prior art as a whole; as noted above, the Examiner considered the claimed invention and clearly considered the art as a whole. Resolving the level of ordinary skill in the art entails considering factors such as problems encountered in the art or prior art solution to those problems; the indication of the level of ordinary skill could be explicitly or implicitly applied in view of the prior art. See MPEP 2141 [R-6] II. In the instant case, the Examiner implicitly applied the indication of the level of ordinary skill. Using liposomes bearing on their surface targeting moieties for DNA delivery was routine in the prior art. Using integrases was routine in the prior art. NCAM was used in the prior art as a targeting moiety. Obviously, it would have been within the capabilities of one of skill in the art to combine such elements to arrive at the claimed invention. MPEP 2141 [R-6] II states:

> "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at ___, 82 USPQ2d at 1396.
>
> In addition to the factors above, Office personnel may rely on their own technical expertise to describe the knowledge and skills of a person of ordinary skill in the art. The Federal Circuit has stated that examiners and administrative patent judges on the Board are "persons of scientific competence in the fields in which they work" and that their findings are "informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art." In re Berg , 320 F.3d 1310, 1315, 65 USPQ2d 2003, 2007 (Fed. Cir. 2003).

With respect to considering objective evidence present in the application, it is noted that there is nothing indicating nonobviousness. The instant specification does not provide more that was known in the art. The only position taken by Applicant is that nobody combined these well known elements before the instant invention was made. However, at the time of the invention, the skills in the art of delivery of therapeutic agents were high, and therefore, one of skill in the art would have known to combine well-known elements with the intent of improving a composition or a method.

Applicant's argument that the instant case is similar to Sanofi-Synthelabo v. Apotex Inc., 550 F3d 1075 (Fed. Cir. Dec. 12, 2008) is not found persuasive. The instant case is not drawn to using individual enantiomers for therapy, wherein there is no scientific principle allowing the prediction of the therapeutic activity of each enantiomer. Liposomes, NCAM, and integrases are not enantiomers; their activity was well known in the prior art, they are combinable, and their combination leads to predictable results, i.e., targeted delivery of DNA to NCAM expressing-cells, followed by the integration of the DNA into the genome. Applicant did not provide any evidence to the contrary.

The reference submitted by Applicant does not provide any additional information indicating nonobviousness. The rejection is not based on using liposomes without a targeting moiety or attaching the targeting moiety via streptavidin-biotin. Furthermore, the prior art already teaches using NCAM for efficient cellular uptake.

9. Claims 1-3, 5, 6, 9, 10, 13, 14, 17, 18, 21-23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of each Sato et al. (J. Drug Target., 2001, 9: 201-207, of record) and Gosselin et al. (Bioconjugate Chem., 2001, 12: 989-994, of record).

The teachings of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. are applied as above for claims 1-3, 5, 6, 22, 23, and 27. Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. do not teach their delivery system as further comprising a DNA compacting agent (claims 9 and 10), nor do they teach a chemical inclusion for breaching the endosomal barrier (claim 21). Sato et al. teach that introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do because the art teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge

(claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., Ranheim et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Sato and Gosselin do not remedy the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons set forth above.

10. Claims 1-3, 5, 6, 22-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al. taken with each Maurer et al., Groth et al., Schreier et al., and Ranheim et al., in further view of Li et al. (Acta Anaesthesiol. Sin., 2000, 38: 207-215, Abstract).

The teachings of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. are applied as above for claims 1-3, 5, 6, 22, 23, and 27. Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. do not teach Bcl-2 delivery (claims 24 and 25). However, doing such is suggested by the prior art which teaches that liposomes can be successfully used to deliver nucleic acids encoding Bcl-2 (see Li et al., Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Groth et al., Schreier et al., and Ranheim et al. by replacing their DNA with a DNA encoding Bcl-2 to achieve the predictable result of delivery Bcl-2 to a subject in need of treatment with anti-apoptotic agents. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 1, 2, 5, 6, 27, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy (U.S. Patent No. 6,635,476, of record), in view of each Poulsen et al., Ranheim et al., and Groth et al.

Murphy teaches a system for the delivery of genes encoding therapeutic polypeptides (i.e., cDNA operably linked to a gene expression construct), the system comprising liposomes having the gene in their internal space and targeting ligands on

their external surface for binding to specific cell surface receptors, wherein the receptors can be NCAM (claims 1, 5, 6, and 28) (Abstract, column 3, lines 5, 6, and 59-63, column 5, lines 24-27, column 9, lines 45-63, column 13, lines 25-46).

Although Murphy teaches NCAM as the cell surface receptor, he does not specifically teach that the targeting ligand is NCAM or an NCAM fragment comprising the first three Ig domains as targeting ligands (claims 1 and 2). Poulsen et al. teach NCAM and NCAM fragments comprising the IgI and IgII domains or the IgIII domain as targeting ligands capable of homophilic binding to another NCAM molecule on the surface of a target cell (p. 3, paragraph 0036, p. 4, paragraphs 0048-0051, p. 28, paragraphs 0288 and 0290, p. 29, paragraphs 0355, p. 31, paragraphs 0358-0360). It would have been obvious to one of skill in the art, at the time the invention was made, to modify Murphy's delivery system by using one of the targeting ligands taught by Poulsen et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Murphy teaches delivery to cells expressing NCAM on their surface and because Poulsen et al. teach their fragments as capable of specific delivery to NCAM-expressing cells. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because Murphy teaches that any ligand that binds NCAM can be used with their system (column 13, lines 50-61). With respect to the limitation recited in claim 2, it would have been obvious to one of skill in the art, at the time the invention was made, to combine the IgIII and IgI+IgII fragments of Poulsen et al. to obtain an IgI+IgII+IgIII fragment, for increased binding to NCAM on the target cell surface, with a reasonable expectation of success.

One of skill in the art would have been motivated to do so because the art teaches that, besides the beside IgI and IgII domains, the IgIII domain, also contributes to the binding to NCAM (see Poulsen et al., p. 31, paragraphs 0358-0360; Ranheim et al., p. 4074, column 2, and Fig. 6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that all three Ig NCAM domains are involved in homophilic binding to the NCAM molecule expressed on the surface of the target cell.

Murphy, Poulsen et al., Ranheim et al. do not teach a nucleic acid encoding the phiC31 integrase (claims 1 and 27). However the prior art teaches site-specific integration into mammalian cell genome for research and gene therapy, wherein site-specific integration is used to avoid undesirable mutations in important genes and wherein specific and efficient site-specific integration is achieved by using the phiC31 integrase (see Groth et al., Abstract, p. 5995, column 2, p. 5998, p. 5999, columns 1 and 2, p. 6000, columns 1 and 2). Based on these teachings, one of skill in the art would have known to use phiC31 integrase when the stable and specific integration of genes of interest into the genome of a target cell was required. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al. and Maurer et al. by further including the phiC31 integrase, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain stable and targeted integration of transgenes into a target cell for research or gene therapy purposes. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because

the prior art teaches phiC31 integrase can be successfully used to direct site-specific integration of transgenes into the genome of mammalian cells (see Groth et al., p. 6000, column 1).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Murphy is directed to targeted vectors "that are complexed to a targeting moiety by coordinate covalent linkages mediated by a transition metal ion" (Abstract). Poulsen and Ranheim are discussed above as lacking disclosure related to liposomes comprising DNA integrase activity, and Murphy is also silent regarding DNA integrase activity. Groth is directed to integrase from phi31 to carry out site-specific integration in human cells, but is totally unrelated to NCAM. In the present case, it is clear from the record that it was not predictable whether modifications of Murphy as proposed in the Office Action would exhibit different biological .... activities, and it was also not predictable whether any differences, if any, would be weak, moderate, or strong, or how they would be manifested. The record demonstrates that there was no known scientific principle that allowed prediction of the degree to which different forms of liposomes would exhibit different levels of therapeutic activity. On the basis of this evidence, a person of ordinary skill in this field would not reasonably have predicted that the claimed invention would provide the results of the present invention. The results of the present invention are shown in the accompanying Scientific Report, entitled "Development of Novel Non-Viral Vectors for Gene Therapy of Muscular Diseases," of

which the Applicant is an author. As in Sanofi and Papesch, the present invention is nonobvious over the prior art. Applicant requests that, if the §103 rejection is maintained, or if further rejections are set forth, the Office provide an analysis of obviousness that considers the Graham factors so the Applicants may more readily respond to any assertions of obviousness.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Again, Applicant argues the references individually. The response to such arguments is the same as above. The remaining arguments are the same as above; the response to these arguments is set forth above.

12. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view of each Maurer et al., Smith et al. (U.S. Patent No. 6,329,501, of record), and Charlton et al. (Developmental Biology, 2000, 221: 112-119, of record).

Poulsen et al. teach a delivery system for cDNAs encoding therapeutic proteins (i.e., pharmaceutical agents) the system comprising the cDNAs operably linked to a gene expression construct, a binding partner capable of associating with a cell surface receptor (i.e., a targeting moiety), and polycations, wherein the polycations form particles comprising the nucleic acid in their internal compartment and wherein the polycations form a bridge between the nucleic acid and the targeting moiety, i.e., the targeting moiety is on the particle surface (p. 33, paragraphs 0390-0394, p. 34, paragraphs 0412-0418, p. 39, paragraphs 0563-0565, 0570, 0571, and 0577). Poulsen

et al. teach that the targeting moiety can be NCAM or NCAM IgI+II or IgIII domains (p. 26, paragraph 0264, p. 29, paragraph 0335, p. 30, paragraphs 0346, 0355, and 0357, p. 31, paragraphs 0358-0360).

Although Poulsen et al. teach that liposomes in general could be used to deliver nucleic acids (p. 1, paragraph 0004), they do no specifically teach liposomes as the bridge between the nucleic acid and the targeting moiety (claim 1). Maurer et al. teach liposomes as the leading delivery system for the *in vivo* administration of nucleic acids (Abstract, p. 941, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Poulsen et al. by substituting the polycations with liposomes, with a reasonable expectation of success. The motivation to do so is provided by Maurer et al., who teach liposomes as the leading delivery system for systemic administration of nucleic acids, wherein liposomes are versatile carriers because they can be easily modified by insertion of diverse molecules, such as targeting ligands, to suit any particular application (p. 923, column 1, p. 926, paragraph bridging p. 927, p. 927, column 1, last paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that liposomes can be successfully used to target nucleic acids to the cell/tissue of interest.

Although Poulsen et al. and Maurer et al. teach delivery of therapeutic transgenes, they do not specifically teach a transgene encoding the human dystrophin. Smith et al. teach using liposomes coated with targeted ligands to specifically deliver the dystrophin gene to the muscle cells of patients suffering from Duchenne muscular

dystrophy (Abstract, column 2, lines 50-60, column 5, lines 62-67, column 5, lines 3-10). Although Smith et al. do not specifically teach targeting by using NCAM or a fragment thereof, the prior art teaches that muscle cells express NCAM on their surface (see Charlton et al., Abstract, p. 112, column 2). Based on these teachings in the art as a whole, one of skill in the art would have known that the delivery system of Poulsen et al. and Maurer et al. (i.e., liposomes coated with NCAM or fragments thereof) could be used to deliver transgenes to muscle cells. Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use the system of Poulsen et al. and Maurer et al. to deliver the dystrophin gene of Smith et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to treat patients affected by Duchenne muscular dystrophy, as taught by Smith et al. One of skill in the art would have been expected to have a reasonable expectation of success in using NCAM-coated liposomes to target transgenes to the muscle cells expressing NCAM on their surface because the art teaches that NCAM is involved in homophilic binding to other NCAM molecules (see Poulsen et al., p. 31, paragraphs 0358-0360).

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. Claims 11, 15, 19, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Poulsen et al., in view each Maurer et al., Smith et al., and Charlton et al., in further view of both Sato et al. and Gosselin et al.

The teachings of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. are applied as above for claim 29. Poulsen et al., Maurer et al., Smith et al., and Charlton et al. do not teach their delivery system as further comprising a DNA compacting agent (claim 11). Sato et al. teach that introducing cationic polymers such as high molecular weight PEI into DNA/liposome complexes enhances their transfection efficiency by condensing the DNA and promoting the escape of the DNA from the endosomal compartment (i.e., PEI breaches the endosomal barrier) (p. 202, column 1, last paragraph, and column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the system of Poulsen et al., Maurer et al., Smith et al., and Charlton et al. according to the teachings of Sato et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do because the art teaches that addition of PEI enhance the transfection efficiency of complexes made only of DNA and liposomes.

Poulsen et al., Maurer et al., Smith et al., Charlton et al., and Sato et al. do not teach their PEI as being reversibly cross-linked via a thio bridge (claims 13, 14, 17, and 18). Gosselin et al. teach replacing the cytotoxic high molecular PEI with conjugates consisting of low molecular weight PEI cross-linked via thio bridges, wherein such conjugates are less cytotoxic because the thio bridges are cleaved in the reducing environment of the cytoplasm resulting in less cytotoxic intracellular low molecular weight PEI which has an easier access to the transcription machinery (Abstract, p. 989, column 2, p. 990, Fig. 1 and 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the delivery system of Poulsen et al., Maurer

et al., Smith et al., Charlton et al., and Sato et al. by replacing their high molecular weight PEI with the cross-linked low molecular weight PEI of Gosselin et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain a less cytotoxic DNA delivery system. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that cross-linked low molecular weight PEI can be successfully used to deliver DNA to cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/
Primary Examiner, Art Unit 1633